



We take high pleasure in paying tribute to Larry Garfinkel for his lifelong contribution to the study of smoking and health. Few individuals have contributed as much to our present-day knowledge about the disease consequences of smoking. Since joining the American Cancer Society in 1947, he has played a critical role in this process of discovery, from organizing the earliest prospective studies in the 1950s, to the work that forms the basis of this monograph, and all the important steps in between. I would like to express my deep admiration and appreciation to Larry Garfinkel for his lifelong leadership in combating this Nation's most important health problem.

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# Foreword

This volume presents a detailed and comprehensive picture of the disease consequences that result directly from smoking cigarettes. Concern about the disease risks associated with the use of tobacco dates back two centuries. According to one medical historian, Dr. John Hill (1716?-1775) should be credited with the first report documenting an association between tobacco use and cancer for his work *Cautions Against the Immoderate Use of Snuff*. Others credit J.J. Holland for noting a relationship between cancer of the lip and tobacco use. Soemmering, in 1795, made a similar observation.

By the early part of this century, tobacco use was strongly suspected as a cause of cancer of the mouth because most cases were found among people who either smoked or chewed. However, at the beginning of the 20th century, the disease burden produced by tobacco use was largely unknown, and the staggering epidemic of disease that would be produced by cigarettes was yet to occur. The first successful national marketing of a modern blended cigarette, Camels, occurred in 1913. These new blended cigarettes quickly became the tobacco product of choice among consumers, and the deeper inhalation of tobacco smoke into the lungs that characterized the use of these products transformed the pattern of disease in the United States. Over a relatively short interval, the addictive nature of cigarettes and their widespread acceptance by society resulted in cigarette smoking becoming the largest preventable cause of death and disability in the United States and most of the developed world.

By 1930 a majority of males were already regular cigarette smokers, most having switched to cigarettes around the time of World War I; moreover, the popularity of smoking among females was increasing steadily as social taboos about females smoking gave way in a more “enlightened” era. Lung cancer deaths also began to increase, first among males and then, some 20 to 30 years later, among females. Before 1930 lung cancer was a rare disease not listed on the International Classification of Disease system in the United States. However, by the end of the 1930’s a rapidly increasing lung cancer death rate among males had been noted by several scientists, including Dr. Harold Diehl and cancer surgeon Dr. Alton Ochsner of Tulane University. Dr. Ochsner recalled being aroused from his bed as a third-year medical student to witness a rare medical event that, according to his professors, he would probably not see again in his lifetime—an autopsy of a man who died of lung cancer. As a young cancer surgeon, he saw six lung cancer patients in a single year and concluded that an epidemic of lung cancer must be under way. All these patients were male, and all had a history of heavy cigarette smoking. This observation was among the first to link lung cancer and the new U.S. epidemic of lung cancer.

In 1950 four separate retrospective epidemiological studies demonstrated a clear link between cigarette smoking and lung cancer, and in 1951 two

major prospective mortality studies were initiated in an effort to resolve the remaining scientific questions. Sir Richard Doll and Sir Austin Bradford Hill, under the auspices of the Medical Research Council, enrolled 40,000 British physicians in a prospective study. This cohort now has been successfully followed for 40 years. In the United States, Drs. E. Cuyler Hammond and Daniel Horn, under the aegis of the American Cancer Society (ACS), enrolled 187,783 white males residing in 9 States at the beginning of 1952. In time, a total of 11 prospective mortality studies would form the cornerstone of our knowledge about the disease risks that accompany cigarette smoking. The most recent data from five of these studies are presented in this volume; they once again establish the overwhelming nature of proof that smoking is the largest preventable cause of cancer and other chronic diseases.

Thousands of scientists have contributed to the body of evidence that proves smoking causes disease, including the authors and scientific editors of this volume, but I would like to single out one for his singular dedication and seminal contributions to this field of research.

Assisting Hammond and Horn in their first prospective study was a young scientist named Lawrence Garfinkel. Larry began working for the American Cancer Society in 1947, where he was directly responsible for coordinating much of the field work, including training the thousands of ACS volunteers in data collection techniques. When ACS decided to undertake an even larger study in 1959 by enrolling 1 million people in its Cancer Prevention Study I (CPS-I), Larry's role changed from that of research support to co-principal investigator. He became increasingly involved in both data analysis and publication of results, and in 1961 he coauthored, with Cuyler Hammond, the article "Smoking Habits of Men and Women," which appeared in the August issue of the *Journal of the National Cancer Institute*. This article reported some of the first results from CPS-I.

During the 1960's Larry Garfinkel contributed to more than two dozen major papers on the relationship between smoking and health. (See pages xxvii - xxxiii for a complete chronological list of Mr. Garfinkel's publications.) Along with colleagues Cuyler Hammond and Oscar Auerbach, Larry coauthored the reported results of some of the first studies that combined epidemiology with pathology. These study results appeared in a series of articles in the *New England Journal of Medicine* and provided some of the earliest evidence of smoking's histological damage to the lung. During the 1970's and 1980's Larry wrote more than 70 papers advancing our knowledge of the effects of cigarette smoking on life expectancy, coronary heart disease, and stroke; benefits of quitting smoking; and risks of smoking cigarettes with different tar and nicotine yields.

When Cuyler Hammond retired from ACS in 1979, Larry became director of the ACS research program, and under his guidance, ACS initiated CPS-II, which included participants from all 50 States, the District of Columbia, and Puerto Rico. CPS-II remains the largest epidemiological study of its kind ever attempted in the history of medical science. In 1988 Larry Garfinkel and coauthor Steve Stellman published results on females from CPS-II that

shocked many in public health. Their analyses demonstrated that the lung cancer mortality rate among smoking females in CPS-II had increased nearly fivefold compared with females who smoked in CPS-I. The data for nonsmoking females showed no increase in lung cancer between the two studies—thus providing convincing evidence that lung cancer was almost exclusively a disease found among smokers. Larry Garfinkel is not only a contributor to this monograph; he is also one of its scientific editors.

In closing, I would like to take this opportunity to personally recognize Larry Garfinkel for his lifelong contribution to this important field of scientific inquiry. Few individuals have contributed as much to our knowledge about the disease consequences of smoking as Larry Garfinkel. He has played critical roles in this process of discovery, from organizing the earliest prospective studies to the work that forms the basis of the current volume and all the steps in between. I know I speak not only for the National Cancer Institute but also for the entire scientific community in recognizing Larry's leadership in combating this Nation's most important health problem.

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# Preface

This, the eighth monograph in the Smoking and Tobacco Control series published by the National Cancer Institute (NCI), is in many respects also the most significant. Contained in this volume are new results from five of the world's largest prospective epidemiological studies defining the magnitude of disease risks caused by cigarette smoking.

Thirty years ago, in January 1966, NCI published a similar monograph titled *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. The report of the Surgeon General's Advisory Committee on Smoking and Health had been released in 1964 and had relied extensively on data from prospective mortality studies to delineate the relationship between cigarette smoking and various chronic diseases. The 1966 NCI monograph provided a detailed examination of the outcomes of several of the large prospective mortality studies presented in the 1964 advisory committee report. At that time, the outcomes available from these studies were based on 3 to 6 years of followup; with the exception of the American Cancer Society's (ACS) Cancer Prevention Study I (CPS-I), studies in the 1966 NCI monograph did not include substantial numbers of females. This monograph includes three new prospective mortality studies (CPS-II [Chapter 5], the Nurses' Health Study [Chapter 8], and the Kaiser Permanente Prospective Mortality study [Chapter 6]), provides the outcomes of the CPS-I study after 12 years of followup (Chapter 3), and provides 26 years of followup of the study of U.S. veterans (Chapter 7). Data from these studies provide the most comprehensive description of the disease consequences produced by smoking available to date and are accompanied by a detailed description of the changes in smoking behaviors of the U.S. population over the past century. Prospective mortality studies continue to play a critical role in quantifying the relative mortality risks of smoking for the individual as well as in estimating the overall disease burden caused by cigarette smoking in our society. The goal of this monograph is to facilitate both these tasks by providing, in one volume, comprehensive descriptions of smoking behaviors and the disease risks that result from those behaviors.

**BRIEF HISTORICAL PERSPECTIVE** During the early part of this century, knowledge about the relationship between tobacco use and disease was based largely on clinical observations and a few small case-control studies of patients with lung cancer. A turning point in the understanding of smoking's relationship to disease occurred in 1950 with the publication of four retrospective studies of smoking habits among lung cancer patients and control subjects. Although many epidemiologists were satisfied that the relationship between smoking and lung cancer was established by these retrospective studies, others turned for confirmation to prospective studies that followed large numbers of "healthy" individuals to identify the causes of their subsequent mortality. Facts about an individual's lifestyle (including smoking), family history, medical and occupational data, place of residence,

and other personal information were recorded at the start of such a study and could be related to the frequency with which individuals with these characteristics died of specific diseases.

The first major prospective study was started in Great Britain in 1951 by Sir Richard Doll and Sir Austin Bradford Hill, who enrolled 40,000 British physicians. Doll and colleagues have recently published 40-year followup data on this unique cohort. The first U.S. prospective study was initiated in 1952 by two ACS investigators, E. Cuyler Hammond and Daniel Horn. They enrolled 188,000 white males residing in 9 States. Hammond and Horn released preliminary results from their study at the 103d annual meeting of the American Medical Association in June 1954. The results of these early studies astounded both the medical community and the public.

Significantly elevated death rates among smokers compared to never-smokers were found, not only for lung cancer but also for several other major causes of death. The elevation in risk was much greater for those who smoked cigarettes rather than pipes and cigars, and there was a gradient in risk that increased with the increasing amount smoked.

National Cancer Institute investigator Harold Dorn envisioned an even larger prospective study than that attempted by ACS. In January 1954 Dorn mailed questionnaires on smoking habits to veterans holding U.S. Government life insurance policies. Nearly 300,000 veterans replied; most were veterans of World War I, and almost all policyholders were white males. This cohort has been successfully traced for nearly three decades. The 26-year followup data are reported in this volume (Chapter 7).

Also in 1954 Weir and colleagues started to trace 68,000 California males in various occupations. During 1955 in Canada, Best and colleagues initiated a prospective study involving 92,000 Canadian pensioners. The Canadian Pensioners Study was the first to include significant numbers of females—nearly 14,000. Taken as a group, the prospective studies involved more than 600,000 individuals, but except for the Canadian study, they included few females. In the British Doctors study, only 6,000 enrollees were female, and in the Dorn study of U.S. veterans, less than 1 percent were female.

During 1959 ACS began its Cancer Prevention Study I and purposefully included large numbers of females in the study design. Between October 1959 and April 1960, ACS volunteers enrolled more than 1 million males and females from 25 States (562,671 females and 440,558 males). Participants completed confidential questionnaires about their family medical history, physical complaints, occupations, personal health behaviors, and other factors.

Substantial differences in the disease risks produced by smoking for males compared with those for females were evident in these early epidemiological investigations. For example, based on a 6-year followup from CPS-I, male smokers experienced a 70-percent greater overall mortality risk and a 1,000-percent higher risk from lung cancer than male never-smokers.

However, among females, overall mortality risks were much lower—only 20 to 30 percent higher than that of a never-smoker, and lung cancer mortality among females who smoked was only 200 percent greater than that of never-smoking females. Findings from other prospective and retrospective studies conducted in the United States and abroad during the 1950's and early 1960's confirmed these results.

These differences between males and females found in early epidemiological studies are largely explained by differences in smoking behaviors (Chapter 2). The epidemiological studies were started during the 1950's and 1960's, and the females most at risk for contracting smoking-related chronic diseases in these studies were older and had been born around or prior to the turn of the century. Among the oldest birth cohorts (those born before 1915 and most at risk during the 1950's), there were significant differences between males and females in their total lifetime smoking behaviors. Fifty percent or more of the males born between 1885 and 1915 became regular cigarette smokers at some time during their lives, with some cohorts attaining an ever-smoking rate of 80 percent. No female cohorts attained a smoking rate greater than 45 percent (see Chapter 2), and the very oldest cohorts of these females never exceeded a 20-percent ever-smoking prevalence. There were also important differences in the age at which these cohorts first began to regularly smoke cigarettes. Among males, the majority of ever-smokers had initiated regular smoking before age 21. However, among females born during these early years, smoking initiation frequently occurred as late as their thirties and forties.

This difference between males and females in the age at which they first began to smoke regularly resulted in substantial differences in duration of smoking between males and females in these early prospective studies. Because the magnitude of the risk produced by smoking is closely related to the duration of smoking, the difference in duration of smoking between males and females in the early epidemiological studies translated into differences in the size of the mortality ratios for smokers and never-smokers. Male smokers had longer average durations of smoking at any given age than female smokers, so they also had higher overall mortality ratios. Male smokers also smoked a greater number of cigarettes per day and were more likely to inhale compared with female smokers. These differences in smoking behaviors, rather than a difference in biological susceptibility, explained the apparent difference in the risks of smoking for males and females found in early epidemiological studies.

**RESULTS FROM  
CONTEMPORARY  
STUDIES**

This volume presents results from three large, more contemporary prospective mortality studies and provides longer followup for two of the older studies dating from the 1950's. All these studies contain large numbers of subjects, and with the exception of the U.S. veterans study, all contain large numbers of females. When observations from the more contemporary studies are compared with those from the 1950's, one important but disturbing conclusion is apparent—mortality risks among continuing smokers, both males and females, have increased. In fact, relative

risks for smokers compared to never-smokers have increased for all major smoking-related diseases—coronary heart disease (CHD), lung cancer, other smoking-related cancers, stroke, and chronic obstructive pulmonary disease (COPD). This increase over time in the relative risks for smokers compared to never-smokers has occurred despite a dramatic decline in cardiovascular disease (CVD) death rates in the U.S. population, suggesting that the decline in CVD death rates has been proportionately greater among never-smokers than among continuing smokers.

Perhaps the best example of this can be seen when 6-year followup data from the two ACS studies are compared side by side (Chapter 4). Both CPS-I (initiated in 1959) and CPS-II (initiated in 1982) followed more than 1 million people each. Both used nearly identical study designs and methodologies, and they essentially represent two different groups of smokers born approximately a generation apart. After 6 years of followup, there had been 76,888 deaths among CPS-I participants and 79,802 deaths among CPS-II participants.

The increase in relative risk between the two studies is striking. Relative risks increased for overall mortality and for all the major smoking-related chronic diseases from CPS-I to CPS-II (see Table 1). Lung cancer risk among males who smoked doubled when the two studies were compared, increasing from 11.9 to 23.2. Among females, the lung cancer risk more than quadrupled, increasing from less than 3.0 in CPS-I to 12.8 in CPS-II. Risks for COPD also increased dramatically from 9.3 to 11.7 among males and from 6.7 to 12.8 among females.

The increase in relative risks between CPS-I and CPS-II translates into considerable increases in the percentage of deaths attributable to smoking among current cigarette smokers. Among active smokers, 57 percent of all male deaths and nearly half of all female deaths are attributed to smoking. More than 90 percent of the lung cancer that occurs among smokers is attributable to smoking for both males and females in CPS-II, and 71 percent (male) and 61 percent (female) of other smoking-related cancers are attributed to smoking (see Chapters 4 and 5).

The data for all-cause mortality among females from the Kaiser Permanente study (Chapter 6) and the Nurses' Health Study (Chapter 8) confirm the results found in CPS-II. The Kaiser Permanente study has followed more than 60,000 participants, including 36,035 females, since 1979, whereas the Nurses' Health Study enrolled 121,700 female nurses in 1976.

In both studies, all-cause mortality among females who smoked was 1.9-fold higher than among females who did not smoke. In the Kaiser Permanente study, cause-specific relative risks for female smokers were lung cancer, 15.1; CHD, 1.7; and COPD, 9.0. These findings are nearly identical to those reported for females in CPS-II.

Table 1  
**Changes in cigarette-related mortality risks between Cancer Prevention Study I (1959-1965) and Cancer Prevention Study II (1982-1988) and percentage of deaths attributable to active cigarette smoking**

	CPS-I		CPS-II	
	Males			
	Relative Risk	Percent	Relative Risk	Percent
Overall Mortality	1.7	42.2	2.3	57.1
Lung Cancer	11.9	91.6	23.2	95.7
Coronary Heart Disease	1.7	41.5	1.9	46.2
Chronic Obstructive Pulmonary Disease	9.3	89.2	11.7	91.4
Stroke	1.3	21.9	1.9	46.8
Other Smoking-Related Cancers <sup>a</sup>	2.7	63.4	3.5	71.2
	Females			
Overall Mortality	1.2	18.7	1.9	47.9
Lung Cancer	2.7	63.4	12.8	92.2
Coronary Heart Disease	1.4	27.0	1.8	45.1
Chronic Obstructive Pulmonary Disease	6.7	85.0	12.8	92.2
Stroke	1.2	15.2	1.8	45.7
Other Smoking-Related Cancers <sup>a</sup>	1.8	45.0	2.6	60.8

<sup>a</sup>Sites include larynx, oral cavity, esophagus, bladder, kidney, other urinary, and pancreas.

Based on the previously described differences between males and females in their durations of smoking, the increase in female relative risks was expected as females with longer durations of smoking reached the ages where they were at high risk for disease. However, the increase in relative risk between CPS-I and CPS-II for males was less expected. The increase among males is partly explained by the greater number of cigarettes smoked per day by males in CPS-II compared with CPS-I, and much of the difference between the two sets of relative risks disappears when duration and number of cigarettes smoked per day are held constant.

A difference still persists among smokers of long duration; part of this difference may be explained by the large proportion of males in CPS-I who did *not* start out smoking cigarettes but changed from other forms of tobacco to mass-produced cigarettes just before and during World War I. The modern

blended cigarette did not become popular until 1913 when Camel cigarettes were first introduced. Before their introduction, few people smoked mass-produced, machine-made cigarettes. For example, in 1910, of the 8.59 pounds of tobacco consumed per person in the United States, only 0.41 pound was consumed in the form of machine-made cigarettes (see Figure 1, Chapter 2). In contrast, nearly 4.5 pounds of tobacco were consumed in the form of cigars or as smoking tobacco used in pipes and roll-your-own cigarettes.

**EFFECT OF  
QUITTING  
SMOKING ON  
MORTALITY** This monograph documents in detail the increased disease risks among more contemporary cohorts of cigarette smokers and also sheds considerable light on the positive benefits of quitting. The 26-year followup information from the U.S. veterans study (Chapter 7), as well as data from the other major prospective studies, clearly documents that quitting smoking results in substantial benefits for one's health, regardless of how long or how much one has smoked.

For all-cause mortality, the difference in risk between continuing smokers and those who quit increases with increasing duration of time since cessation. This difference is present when the data on risks are examined as relative risks or as differences in death rates. However, in the veterans study, male smokers had to have quit for 5 years or more before an appreciable reduction in overall mortality was evident. Similar findings are observed among females as well as males in the other epidemiological studies.

The residual risk produced by past smoking in former smokers is less among those who had smoked fewer cigarettes per day compared with those who had smoked two or more packs per day. However, because the death rates among smokers of two or more packs per day are so much higher than the rates for those who smoke one-half pack per day, the difference in death rates between continuing smokers and those who quit is greatest for those who have the greatest risk (heavy smokers). Expressed somewhat differently, the more one smokes, the greater one's risk of disease and, correspondingly, the more risk one can avoid by quitting.

The benefits of cessation are composed of avoidance of the additional risk that accumulates with a longer duration of smoking and the reversal of risk with increased years off cigarettes. Heavy smokers appear to retain some degree of elevated risk for lung cancer when compared to never-smokers, even after 20 years of cessation. In contrast, the risks for CHD for heavy smokers may eventually return to those of never-smokers after 20 years of cessation. Among veterans who reported smoking two or more packs of cigarettes daily and who had quit smoking for more than 30 years, overall mortality was still slightly elevated compared to never-smokers; a similar result was evident for smokers of more than two packs per day in the CPS-I study. For both studies, no excess overall mortality was demonstrated for light smokers who had quit for 20 years or more.

**PUBLIC HEALTH IMPLICATIONS** This volume presents the most detailed and comprehensive epidemiological description of the disease consequences of smoking ever assembled in one publication. It once again strongly reinforces what the public health community has been saying for more than 40 years: The best, and possibly the only, way to avoid the death and disability caused by cigarette smoking is to never begin, and the return on public health interventions that prevent smoking initiation, although a long time in arriving, is enormous.

For those who do start smoking, the less they smoke and the sooner they quit, the more risk they can avoid. Heavy smokers and smokers of longer duration are at greatest risk, but correspondingly, they also have the most to gain from cessation.

Preventing adolescent onset of regular smoking may have the greatest benefit for the individual and society in the long run, but it often takes decades before prevention has any measureable effect on national death rates. That option is not available to the nearly 50 million adult Americans who currently smoke cigarettes: The benefits of cessation will take 30 or more years before they affect U.S. death rates. The benefits of cessation are available to individuals who currently smoke, are greatest for those at greatest risk, and can affect death rates in as little as 5 years.

The clearest message that is drawn from the enormous quantity of data presented in this monograph is that smoking prevention and cessation efforts are complementary, not alternative, solutions to the current epidemic of diseases caused by smoking. We must accomplish both prevention and cessation if we are to successfully reduce the tragic burden of death and disability currently produced by cigarette smoking.

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